Title
The effects of one-hour wear of high-Dk soft contact lenses on corneal pH and epithelial permeability.

Journal
The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc, 26(3)

ISSN
0733-8902

Authors
Lin, MC
Graham, AD
Polse, KA
et al.

Publication Date
2000-07-01

Peer reviewed

The Effects of One-Hour Wear of High-Dk Soft Contact Lenses on Corneal pH and Epithelial Permeability

Meng C. Lin, OD Andrew D. Graham, MS Kenneth A. Polse, OD, MS
Nancy A. McNamara, PhD Timothy G. Tieu, BS

Purpose: **Previous studies have shown that 1-hour closed-eye contact lens wear with a low-Dk lens causes a significant reduction in corneal pH and an increase in epithelial permeability. In the present study, we evaluated the effects of super-high-Dk/t soft lenses on corneal epithelial barrier function and stromal pH.**

Methods: **Corneal thickness was measured by optical pachometry, while epithelial permeability and stromal pH were measured by fluorophotometry. A paired-eye design was used in which one eye was randomly allocated to wear a high-oxygen-permeable soft lens (CIBAVision Focus®/NIGHT & DAY™ (Dk/t= 175) while the other eye did not wear a lens.**

Results: **After 1-hour closed-eye lens wear, neither the difference in corneal swelling (*P* = 0.206) nor the permeability (*P* = 0.055) between both eyes was significantly different. The mean pH values under open-eye conditions were 7.66 vs. 7.57 for the treatment and control eyes, respectively (*P* = 0.082), dropping to 7.27 vs. 7.25 after 1-hour eye closure (*P* = 0.283).**

Conclusions: **Although our results are limited to a 1-hour observation period, they do provide evidence that high-Dk materials may eliminate corneal acidosis and reduced epithelial barrier function that accompany closed-eye contact lens wear with lower-Dk soft lens materials.**

Introduction

Soft contact lens extended wear has been shown to be associated with the development of several ocular complications, some of which can potentially reduce vision.[1-2] There is evidence that some of these complications are caused by corneal hypoxia which occurs during closed-eye contact lens wear,[3] resulting in a substantial effort to develop a high oxygen (Dk) and carbon dioxide permeable soft lens material. Recently, a fluorosiloxane co-polymer was developed that has an oxygen permeability of 140×10^{-11} (cm²/sec)(mL x O_2/(mL x mmHg)). When this lens is manufactured with an average thickness of 80 µm, the resulting oxygen transmissibility (Dk/t) is approximately 175×10^{-9} (cm x mL x O_2)/(sec x mL x mmHg).[4] Estimates from previous studies suggest that this high level of Dk/t should be sufficient to prevent corneal edema under both open- and closed-eye conditions.[5] Recent pachometry studies have confirmed that high oxygen permeable lenses worn under both open- and closed-eye conditions do not alter corneal thickness from physiological levels measured when the lens is not present.[6]

The lack of edema induced by these new high-Dk/t lenses has prompted us to look for more information about other physiological effects that these lenses may have on the cornea. Additional data on the effects of high-Dk lenses may be important since there is very little substantive information to show that changes in corneal thickness induced by hypoxia are solely responsible for the ocular complications associated with soft contact lens extended wear. For example, there are reports which show that closed-eye contact lens induced corneal acidosis has been associated with a decrease in corneal hydration control and changes in endothelial cell morphology.[7-9] Also, we have recently demonstrated that wearing standard disposable soft lenses for one hour with eyes closed resulted, on average, in a 40% increase in epithelial permeability (P_{dc}).[10] However, when the eye is exposed to hypoxia alone for one hour without the presence of a soft lens in the eye, corneal thickness is increased without a corresponding change in P_{dc}.[11] What is not known is whether closed-eye wear with high Dk/t lenses for one hour will alter stromal pH and P_{dc}.

The pH and P_{dc} measurements may provide new indicators of subtle changes in corneal structure and function associated with contact lens wear that may not be detectable using standard investigational techniques (e.g., pachometry, slit lamp assessment). These findings provide the basis for our current study, which is designed to explore the effects of high-Dk/t soft lenses on corneal pH and epithelial barrier function. We used a paired-eye paradigm to test the hypothesis that high-Dk/t lenses do not alter corneal pH or epithelial barrier function, resulting in new information about the physiological effects of corneal hypoxia induced by contact lens wear.

Materials and methods

Subject Recruitment and Randomization: A total of 43 subjects between the ages of 18 and 28 participated in the study. Subjects were eligible if they were: 1) between the ages of 18-39; 2) free from ocular disease; 3) not currently wearing contact lenses; 4) not currently taking medications known to alter the integrity of the cornea or quality of the tear film; and 5) not suffering from seasonal allergies. We enrolled 40 subjects in Part 1 of the study (corneal thickness and epithelial permeability measurements) and 16 subjects in Part 2 (corneal pH measurements). Of the 16 subjects, 13 also participated in Part 1 of the study. In both parts of the study we employed a paired-eye strategy in which each subject received the high-Dk/t lens in one eye (treatment) and no lens in the other eye (control).

The eye to receive the study lens and the eye to be measured first were independently randomized for each subject to control for possible bias due to systematic differences between right and left eyes or due to measurement sequence. A full explanation of the study procedures was given to each subject and informed consent was obtained. This study observed the tenets of the Declaration of Helsinki and was approved by the University of California, Berkeley, Committee for Protection of Human Subjects.

Soft Lens Material: Study lenses were manufactured using a recently developed fluorosiloxane hydrogel material (CIBA Vision Focus® / NIGHT & DAY™ with a water content of 24% and a Dk/t of 175 x 10^{-9} (cm x mL x O_2)/(sec x mL x mmHg). Lens parameter specifications (power = -2.00DS, diameter = 14.0 mm and average center thickness = 80 μm) were the same for all subjects.

Instrumentation: Corneal thickness measurements were taken with a modified Haag-Streit optical pachometer equipped with small light-emitting diodes (LEDs) to improve patient fixation and alignment. For each pachometry measurement 20 replicate readings were taken within a period of 2-3 minutes and then averaged. An automated scanning fluorophotometer (Fluorotron™ Master, Ocumetrics, Mountain View, CA) was used to measure corneal epithelial permeability to fluorescein (P_{dc}). The fluorescein dye was instilled using a single-drop application technique. To measure in vivo human corneal pH, the Fluorotron Master was modified to include two rapidly alternating blue-filtered LEDs. Stromal pH was obtained by loading the cornea with fluorescein, exciting the dye at 450 and 490 nm by rapidly modulating the two LEDs as the subject fixates on them, and measuring the resulting fluorescence emission intensity. The ratio of the fluorescence emission intensity from the 490 and 450 nm wavelengths is pH sensitive.[12] The pachometer calibration and measurement techniques, the Fluorotron Master and single-drop technique for P_{dc} measurement, and the modified Fluorotron pH instrument are all described in detail elsewhere.[13-16]

Procedures—Part 1: Measurements of Corneal Thickness and Epithelial Permeability To Fluorescein (P_{dc}): A total of 40 subjects participated in this phase of the study. Baseline corneal thickness and auto-fluorescence measurements were made after subjects had been awake a minimum of 2 hours. After the baseline readings, the high-Dk/t lens was inserted in the eye randomized to treatment. Ten minutes after lens insertion, the lens fit was assessed. Criteria for an acceptable lens fit included full corneal coverage, adequate movement, and a satisfactory subjective comfort rating. After the assessment of the lens fit, subjects were placed in a supine position and instructed to close their eyes. Following 1-hour closed-eye lens wear the lens was then removed and pachometry readings were obtained. These measurements required 3-5 minutes and were immediately followed by the epithelial permeability assessments. At the completion of the P_{dc} measurement, an observer who was masked to the randomization scheme carried out a slit lamp examination using both white and blue light to assess corneal integrity. The presence of corneal staining with fluorescein was graded on a 1 to 4 scale using a previously reported system.[17] Punctate staining of fewer than five points was graded as 1; 5 to 10 points as grade 2; 11 to 25 points as grade 3; and more than 26 points as grade 4. Linear staining was considered to be a row of punctate points and was graded accordingly. Subjects exhibiting grade 1 or greater epithelial disruption in the central cornea were excluded from the analysis to avoid an overestimate of P_{dc} value.

Part 2: Measurements of Corneal pH: A total of 16 subjects, 13 of whom also participated in Part 1, were enrolled in this phase of the study. Following a slit lamp examination and corneal auto-fluorescence readings, 4-6 drops of 5% non-preserved sterile fluorescein solution (Fluorescite® Injection, Alcon Laboratories, Inc.) were instilled onto the superior bulbar conjunctiva of each eye over a period of 30-40 minutes to allow adequate penetration into the corneal stroma. The eyes were then thoroughly irrigated using a sterile, preservative-free saline solution (UNISOL® solution, Alcon Laboratories, Inc). After irrigation we allowed for a ten-minute waiting period before beginning the open-eye pH measurements to ensure that the subject was comfortable and ready to concentrate on maintaining the accurate fixation necessary for the pH measurement. After the open-eye readings, the eye randomized to treatment received the high Dk/t contact lens. After 30 minutes of lens wear, the lens was removed briefly for a second set of open-eye pH readings, then it was re-inserted and the subject placed in the supine position with the eyes closed for one hour. After the 1-

TABLE I Mean ± SE changes in corneal thickness and epithelial permeability after one hour of eye closure. Paired-t test compared percent change in corneal thickness (Δ% CT) and natural log of epithelial permeability (ln [P_{dc}]) between control and treatment eyes.

	Δ% CT (µm)	ln(P_{dc}) (ln[nm/sec])
Control	3.14% ± 0.30	-2.68 ± 0.09
Treatment	3.57% ± 0.30	-2.88 ± 0.10
P-value	0.206	0.055

hour eye closure, the lens was again removed and pH readings taken on both eyes. For each pH measurement we obtained three readings within a 60-90 second observation period.

Results

Part 1: Measurements of Corneal Thickness and Epithelial Permeability to Fluorescein (P_{dc}): Of the 40 participants who completed the permeability measurements we excluded eight subjects from the data set. Two of these subjects had negative P_{dc}, which was likely a result of a lower post-rinse stromal fluorescence compared to the background fluorescence for the same eye. Six subjects showed 1+ or greater central corneal staining, which might bias a P_{dc} estimate. This provided a total of 32 subjects, an adequate sample size, for the epithelial permeability analysis.[15]

Table I provides information on changes in corneal thickness and epithelial permeability after 1-hour closed-eye lens wear for both the control and treatment eyes. The mean ± SE changes in corneal thickness after one hour of eye closure were 3.14 ± 0.3% and 3.57 ± 0.3% for the control and treatment eyes, respectively. The increase in corneal thickness from baseline after one hour of eye closure was significant ($P < 0.0001$) for both eyes, while the difference in mean corneal swelling between the control and treatment eyes was not significant ($P = 0.206$).

Before statistical analysis the natural log (ln) transformation was applied to the epithelial permeability estimates to stabilize the variance and to better approximate normality. In Table I, the mean ± SE ln(P_{dc}) measured in the treatment eye was -2.88 ± 0.10 compared to -2.68 ± 0.09 for the control eye (higher negative value = better epithelial barrier function). Back-transformation of the mean ln(P_{dc}) gave approximate median P_{dc} estimates for the treatment and control eyes of 0.056 nm/s and 0.069 nm/s, respectively.

Part 2: Measurements of Corneal pH: With 16 subjects measured under baseline, open-eye, and closed-eye conditions in this phase of the study, there were 96 possible sets of three pH readings (16 subjects x 2 eyes x 3 conditions). Since pH values were obtained by rationing between two wavelengths (490 nm and 450nm), any blinking or change in measuring angles during the duration of the scan could lead to extreme readings. We therefore chose to omit data that were beyond physiological limits (< 6.5 or > 8.0 pH units). Using this exclusion criterion, we were able to obtain at least two usable pH values in all but four sets of measurements, and at least one good reading in 3 of those 4 sets.

TABLE II Mean ± SE corneal pH for both eyes open with no lens on either eye (baseline) and after 30-minute open eye and one-hour closed eye with treatment eye wearing experimental soft contact lens. Paired t-test compared the mean pH values between control and treatment eyes under baseline, open-eye, and closed-eye conditions.

	Baseline	Open eye	Closed eye
Control	7.59 ± 0.04	7.66 ± 0.04	7.27 ± 0.03
Treatment	7.54 ± 0.03	7.57 ± 0.03	7.25 ± 0.02
P-value	0.268	0.082	0.283

Table II summarizes the pH results for control and treatment eyes under all testing conditions. We first measured the baseline pH in both eyes and found the sample means ± SE to be 7.59 ± 0.04 and 7.54 ± 0.03 for the control and treatment eyes, respectively. After the baseline pH measurements, the high-Dk/t lens was inserted in the treatment eye and the lens was worn with both eyes open for 30 minutes and then closed for one hour. This allowed us to compare stromal pH between control and treatment eyes under open- (7.66 ± 0.04 vs. 7.57 ± 0.03) and closed-eye conditions (7.27 ± 0.03 vs. 7.25 ± 0.02). These small differences in pH between fellow eyes in both the open- and closed-eye conditions are similar to those that occur under normal open- and closed-eye conditions (i.e., without lens wear); they are neither clinically important nor statistically significant (*P*-values of 0.082 and 0.283, respectively).

The pH data shown in Figure 1 were taken under open- and closed-eye conditions of the same subject. The data were connected by a straight line for both the control and treatment eyes. There were significant decreases in pH values ($pH_{open} - pH_{closed}$) of 0.39 (*P*-value < 0.0001) and 0.32 (*P*-value < 0.0001) in the control and treatment eyes, respectively. The change in pH from the open- to closed-eye conditions did not differ significantly

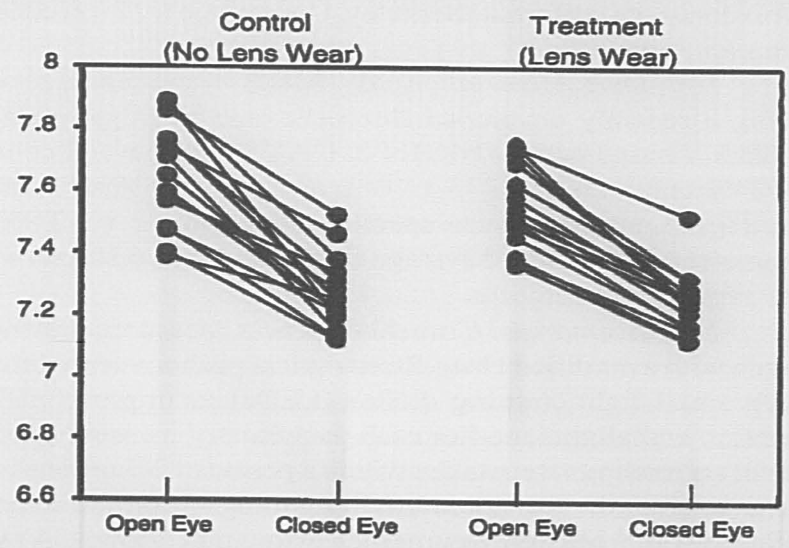

Figure 1 *pH measurements obtained for the control (no lens wear) and treatment (with lens wear) eyes in the open- and closed-eye conditions. Measurements of each eye under open- and closed-eye conditions are connected with a straight line.*

between the control and treatment eyes (P-value = 0.127).

Discussion

This study shows that the changes in epithelial permeability and stromal pH observed while wearing standard disposable soft contact lenses may be eliminated when high-oxygen-permeable lenses are worn. These results provide evidence that the reduced epithelial barrier function and corneal acidosis, which occur during closed-eye wear, are likely caused in part by corneal hypoxia. This conclusion seems plausible because previous work has shown that the minimum oxygen transmission necessary to maintain normal corneal metabolism (i.e., to prevent corneal edema) during closed-eye wear is 87×10^{-9} (cm x mL x O_2)/(sec x mL x mmHg)).[5,18] The lenses used in this study exceed that minimum by at least two-fold compared to standard disposable soft lenses, which provide less than one-third of the required oxygen needed for normal corneal metabolism during eye closure. Even though this study shows that one hour of closed-eye wear has little effect on corneal pH or epithelial barrier function, it will be important to explore the effect of high-Dk/t lenses on pH and P_{dc} over longer wearing periods (e.g., 8 hours of overnight wear).

We noted that the differences in the corneal swelling responses were similar between the two eyes and in agreement with that of eye closure without lens wear.[19] However, a recent report has shown that when these high-Dk/t materials are worn using a similar paired-eye paradigm, there is a significantly less corneal swelling in the control (non-lens wearing) eye compared to the treatment (lens wearing) eye.[6] In the present study we did not encounter significantly less swelling in the control eye compared to the treatment eye; however, our study used a 1-hour paradigm while the other investigator measured corneal thickness after 8 hours of eye closure. It is possible that it takes several hours of eye closure (with sleep) to induce this sympathetic "thinning" effect.

In our study we also noted a modest increase, on average, in epithelial barrier function in the lens-wearing eye. While this result is difficult to explain, there is some recent evidence in which cell apoptosis is reduced after the wearing of high-oxygen-transmissible soft lenses compared to the control eye.[20] Although our results suggest that high-Dk lenses do not compromise epithelial integrity, further work is necessary before we can verify that high-Dk lenses worn under closed-eye conditions actually offer some protective effect.

The open- and closed-eye pH values (no lens) are in agreement with previous measurements.[12] However, we did encounter a modest increase of 0.07 pH units for the control eye between the baseline and open-eye conditions. This significant shift in pH (P-value = 0.03) cannot be easily explained on a physiological basis because the baseline and open-eye testing conditions were identical for the control (no lens) eye. Previous work has shown that the repeatability of the pH fluorophotometer is excellent and therefore we are unable to explain this difference based on instrument variability.[16]

In summary, we believe that super-high-Dk/t materials will eliminate corneal hypoxia and associated corneal responses (e.g., stromal acidosis, increased P_{dc}, corneal swelling). However, there are other potential risk factors that may adversely affect the ocular response to extended lens wear such as insufficient tear exchange under the lens, adherence of bacteria and other microorganisms to the lens surface and corneal epithelium, poor lens movement, and inadequate post-lens tear film thickness. Therefore, it is important that additional clinical and laboratory testing be done to more completely assess the safety of these lenses for long-term extended wear.

References

1. Poggio EC, Glynn RJ, Schein OD, et al: The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. *N Engl J Med* 1989;321:779-783.
2. Schein OD, Glynn RJ, Poggio EC, et al: The relative risk of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. A case-control study. Microbial keratitis study group. *N Engl J Med* 1989;321:773-778.
3. Bonanno JA, Polse KA: In: Tomlinson A, (ed). *Complications of Contact Lens Wear*. Chicago: Mosby-Year Book, 1992:21-36.
4. Alvord L, Court J, Davis T, et al: Oxygen permeability of a new type of high Dk soft contact lens material. *Opt and Vis Sci* 1998;75(1):30-6.
5. Holden B, Mertz G: Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. *Invest Ophthalmol Vis Sci* 1984;25:1161-1167.
6. Fonn D, du Toit R, Situ P, et al: Apparent sympathetic response of contralateral non-lens wearing eyes after overnight lens wear in the fellow eye. *Invest Ophthalmol Vis Sci* 1998;39(4):S336(1559-B440).
7. Polse KA, Brand RJ, Cohen SR, et al: Hypoxic effects on corneal morphology and function. *Invest Ophthalmol Vis Sci* 1990;31(8):1542-1554.
8. Polse KA, Rivera RK, Gan CM, et al: Contact lens wear affects corneal pH: Implications and new directions for contact lens research. *J Brit CL Assn* 1992;15(4):171-177.
9. Rivera R, Gan C, Polse K, et al: Contact lenses affect corneal stromal pH. *Opt & Vis Sci* 1993;70(12):991-997.
10. McNamara NA, Fusaro RE, Brand RJ, et al: Epithelial permeability reflects subclinical effects of contact lens wear: *Brit J Ophthalmol* 1998;82(4):376-381.
11. McNamara NA, Chan JS, Han SC, et al: Effects of hypoxia on corneal epithelial permeability. *Am J Ophthalmol* 1999;127(2):153-157.
12. Bonanno JA, Polse KA: Measurement of in vivo human corneal pH: Open and closed eyes. *Invest Ophthalmol &Vis Sci* 1987;28(3):522-530.
13. Mandell RB, Polse KA: Keratoconus. Spatial variation of corneal thickness as a diagnostic test. *Arch Ophthalmol* 1969;82:182-188.
14. Mandell RB, Polse KA, Bonanno J: Reassessment of Optical Pachometry. In: Cavanagh HD, (ed). *The Cornea: Transactions of the World Cornea on the Cornea III*. Raven Press, 1988:201-205.
15. McNamara NA, Fusaro RE, Brand RJ, et al: Measurement of corneal epithelial permeability to fluorescein: A repeatability study. *Invest Ophthalmol & Vis Sci* 1997;38(9):1830-1839.
16. Ishimoto BM, Graham A, Lin MC, et al: A new fluorotron for the measurement of corneal pH. *Invest Ophthalmol & Vis Sci* 1999;40(4):S909(4797-B600).
17. Begley CG, Weirich B, Benak J, et al: Effects of rigid gas permeable contact lens solutions on the human corneal epithelium. *Optom Vis Sci* 1992;69:347-353
18. Harvitt D, Bonnano J: Minimum contact lens transmissibility value for daily and extended wear contact lenses. *Opt and Vis Sci* 1998;75(12S):189.
19. Mandell RB, Fatt I: Thinning of the Human Cornea on Awakening. *Nature* 1965;Oct.16;208:292-293.
20. Cavanagh HD, Ren H, Ladage PM, et al: Effects of low and high Dk daily contact lens wear on binding of *Pseudomonas aeruginosa* to human corneal epithelium. *Invest Ophthalmol & Vis Sci* 1998;39(4):S906(4778-B581).

From the Morton D. Sarver Laboratory for Cornea and Contact Lens Research, School of Optometry, University of California, Berkeley, CA 94720-2020.

Correspondence to: Meng C. Lin, OD, School of Optometry, University of California, Berkeley, CA 94720-2020

Accepted for publication February 21, 2000.